REMARKS

1. Status of the Claims

Claims 1-75 are pending. Claims 1, 2, 9, 15, 16, 21, and 22 are herein amended. Claims 4-8, 11, and 74-75 are herein cancelled. New claim 75 is added.

Claim 1 is amended. Support for this amendment is found in the Specification on page 10, line 25; page 15, lines 10-15, and from page 21, line 21 to page 22, line 5.

The amendments to claims 2, 9, 15, 16, 21, and 22 are made to make those claims consistent with claim 1.

Claim 15 is amended to correct a typographical error.

New claim 75 is added. Support for claim 75 is found in the Specification at page 20, lines 14-16.

2. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1-24 and 73-74 as indefinite.

The Examiner rejects claim 1 for the recitation of "prodrug lipid derivative" stating that it is unclear what the drug is in the composition. Applicants have amended claim 1 to clarify the presently claimed composition. For instance, claim 1 recites lipid derivatives that are substrates of PLA_2, R_3 is naturally occurring hydrophilic moieties, and R_1 and R_2 are both saturated alkyl chains. Applicants submit that this amendment overcomes the rejection. Applicants request that it be withdrawn.

The Examiner rejects claim 4 for lack of antecedent basis for "organic radical." Claim 4 has now been cancelled, thereby obviating the rejection.

The Examiner rejects claim 6 as not further limiting the parent claims. Claim 6 has now been cancelled, thereby obviating the rejection.

3. Rejection under 35 U.S.C. § 103, Obviousness

3.1 Hong 392, Hong 911, and Peterson

The Examiner rejects claims 1-11, 14-24, and 73-74 as unpatentable over Hong (392), Hong (911), or Peterson in combination with Janjic (US 6,229,002) and Vermehren (BBA, 1998). The Examiner also rejects claims 12, 13, and 22 as being unpatentable unpatentable over Hong (392), Hong (911) or Peterson, as applied to claims 1-11, 14-24, and 73-74, further in view of Saxon or Bally. Applicants submit that the Examiner has not established a *prima facie* case of obviousness. Therefore, Applicants respectfully traverse.

3.1.1 Hong 911 in combination with Janjic and Vermehren

Hong 911 teaches nucleoside 5'-diphosphate conjugates of ether lipids. The compounds of Hong 911 are intended for antiviral therapy and therefore it is preferred that they are taken up by the cells of the RES (Reticulo-Endothelial System) such as monocytes and macrophages (Hong 911, column 5, lines 19-35). This can be accomplished by a liposomal formulation as described in lines 23-24, column 5. However, if lipopolymers are included in the liposomes the liposomes will avoid cells of the RES (see Specification of present Application, page 24, line 19 to page 25, line 2; page 26, line 15-16). In contrast, the present invention is intended to avoid uptake by the RES (see Specification of present Application, page 24, line 19 to page 25, line 2). Thus, Hong 911 *teaches away* from the present invention, which includes polymers in the liposomes.

Furthermore, the skilled person will find no motivation to combine the teachings of Hong 911 with Vermehren or Janjic, both references teaching that the inclusion of polymers prevents the removal of liposomes by phagocytic cells of the RES.

Even if the skilled person was to combine Hong 911 with Vermehren or Janjic, he would not arrive at the present invention as defined in the claims. Instead he would arrive at liposomes

comprising a lipopolymer (from Janjic) and prodrugs of *antiviral compounds* (nucleoside 5' diphosphates, from Hong 911, prodrugs from Vermehren). Nothing suggests the prodrug of the present invention.

Thus one of skill in the art would not combine Hong 911 with either Vermehren or Janjic to find the present invention obvious. Applicants request that the rejection be withdrawn.

3.1.2 Hong 392 in combination with Janjic and Vermehren

The Examiner states that Hong 392 teaches thiophospholipid conjugates of antitumor agents and teaches that these cytotoxic drugs can form liposomes. It is also taught that anticancer nucleosides can be releasable *within the cell* via phospholipid-enzyme specific reactions.

Hong 392 does not describe a prodrug, wherein the prodrug is activated by PLA_2. Consequently, Hong 392 describes many compounds which are not substrates for PLA_2, e.g., where A_2 (corresponding to the 2-position) is O, S, or Se.

Additionally, Hong 392 does not teach phospholipid conjugates where A_1 (corresponding to the 1-position) comprise O, i.e., an ether linkage as described for the prodrug of the present invention.

Hong 392 also does not give any indication of insufficient stability or half-life of liposomes in the blood, and does not mention any reason to avoid uptake of liposomes by cells of the RES. Thus, a skilled artisan would not have looked to Janjic to provide solutions to unknown problems. Moreover, Hong 392 does not describe a prodrug concept based on PLA_2 hydrolysis. Hence one of skill in the art would not have looked to Vermehren.

Even if Hong 392 is combined with Janjic or Vermehren, the skilled artisan would not arrive at the present invention as defined in the claims. Instead, one of skill in the art would be directed to produce a liposome comprising a lipopolymer, thiophospholipids, and prodrugs of nucleosides;

not the composition of the present invention. Applicants request that this rejection be withdrawn.

3.1.3 Peterson in combination with Janjic and Vermehren

Peterson describes anti-tumor retinoid phospholipid conjugates with a fatty ether substituent, a retinoid ester substituent and a phosphoethanolamine substituent. Peterson mentions that the compounds may be formulated in liposomes.

Peterson does not describe a prodrug concept, wherein the prodrug is activated by PLA_2. In accordance with this, most compounds described by Peterson are not substrates for PLA_2, e.g. where the 2-position is substituted with a fatty ether substituent or with a phosphorethanolamine substituent.

Peterson also does not give any indications of insufficient stability or half-life of liposomes in the blood and does not mention any reason to avoid uptake of liposomes by cells of the RES. Therefore, the person skilled in the art will find no motivation to look for solutions to such undisclosed problems and, consequently, he would not combine Peterson with Janjic. Moreover, Peterson does not describe a prodrug concept based on PLA_2 hydrolysis. Hence, there is no motivation to combine Peterson with Vermehren.

Even if Peterson is combined with Janjic or Vermehren, the skilled artisan would not arrive at the present invention as defined in the claims. Instead he would arrive at liposomes comprising a lipopolymer and phospholipid conjugates with a fatty ether substituent, a retinoid substituent, and a phosphoethanolamine substituent.

3.2 Kozak

The Examiner rejects claims 1-11, 14-24, and 73-74 as unpatentable Kozak in combination with Janjic (US 6,229,002), and Vermehren (BBA, 1998). The Examiner also rejects claims 12, 13, and 22 as being unpatentable with the three references, as applied to claims 1-11, 14-24, and 73-

74, further in view of Saxon or Bally. Applicants submit that the Examiner has not established a *prima facie* case of obviousness. Therefore, Applicants respectfully traverse.

3.2.1 Kozak in combination with Janjic and Vermehren

Kozak describes prodrugs with enhanced penetration into cells. Preferably, the prodrug is a protease inhibitor conjugated to a phospholipid. According to Kozak, the protease inhibitor is preferably a calcium chelating agent. It is preferred that the prodrugs are activated by intracellular enzymes, e.g., PLA_2. Kozak does not teach lipids, wherein X is 0 or S (1-position is ether or thioether), i.e., Kozak does not teach prodrugs of lyso-etherlipids.

Additionally, Kozak teaches away from the present invention because, Kozak specifically teaches that it is not desirable to formulate prodrugs into liposomes since this achieves preferential distribution to specific organs and cells (Kozak, column 6, lines 4-8). Kozak does not mention that the reason why liposomes are undesirable is to avoid uptake by the RES. Kozak simply teaches that the distribution achieved using liposomes is undesirable, and the skilled person would not read this as being directed to avoidance of RES uptake. In conclusion, the skilled artisan would not combine Kozak with Vermehren or Janjic.

Even if the skilled person was to combine Kozak with Vermehren or Janjic, he would not arrive at the present invention as defined in the claims. Instead, he would arrive at liposomes comprising a lipopolymer and a prodrug of a protease inhibitor. Thus Applicants request that the rejection be withdrawn.

3.4 Saxon and Bally

The Examiner rejects 12, 13, and 22 as unpatentable over Hong (392), Hong (911), Peterson, or Kozak in combination with Janjic (US 6,229,002) and Vermehren (BBA, 1998) and further in light of Saxon and Bally. The Examiner cites Saxon and Bally for the teaching that anticancer drugs can be used in combination in liposomes. However, neither Saxon nor Bally add anything to the analysis above. Thus, though both references mention combination therapy, they does not

render obvious the liposomal drug delivery system of the present invention. Since, as discussed above, the drug delivery system itself is not obvious, the instant rejection should be withdrawn.

3.4 Unexpected Results

Though the Examiner has not met the burden to establish *prima facie* obviousness, Applicants submit that the unexpected characteristics of the present invention rebut any such showing. The present invention takes advantage of:

a) the ability of PLA_2 to hydrolyse ether lipids into lyso-etherlipids,
b) the cytotoxic properties of lyso-etherlipids, as well as
c) the surprising membrane permeability enhancing properties of these molecules, which can lead to enhanced drug diffusion into cells.

Prodrugs of lyso-etherlipids as described in the present invention display a very low haemo-toxicity, which has been a major obstacle for ether lipids in cancer therapy. The *in vivo* data of the invention shows that compared to the lyso-etherlipid of the prior art which killed 5/5 mice within 30 minutes of administration, the present invention killed none, in the same time period. (See Figure 6, and page 7, lines 12-25 and particularly Example 18). Thus, the present invention is surprisingly non-toxic compared to the prior art disclosing treatment with lyso-etherlipids.

When comparing the present invention against the activities of other lipid delivery systems, the present invention also displays the surprising characteristic in that these molecules increase drug release from liposomes and increased membrane permeability, all catalyzed by *extracellular* PLA_2. (See Specification page 47, line 22 to page 48, line 4). Furthermore, the liposomal drug-delivery system of the present invention synergistically reacts with the *extracellular* PLA_2 to increase the drug release and membrane permeability, thereby delivering more drug to the targeted cell. (*Id.*). In contrast, Hong 392 (col. 2, line 31), Kozak (abstract and throughout), and Hong 911 (col. 2, lines 52-54) all discuss cleavage by *intracellular* PLA_2. (Peterson does not disclose the prodrug concept at all, nor does it discuss cleavage by PLA_2.). Thus one skilled in the art would not have expected that the liposomal drug delivery system of the invention would

be more effective than other liposomal drug-delivery systems to increase drug release and membrane permeability.

Since lyso-etherlipids released from lipid derivatives by PLA_2 in the extracellular environment of tumor cells have membrane permeability enhancing properties, the invention also enables combining a prodrug concept and improved drug-delivery in a single liposome.

None of the cited references, neither separately nor in any combinations, describe the products of the present invention or would lead one of skill in the art to expect that the present invention would be effective, while having such a low toxicity.

4. Conclusion

Favorable action and early allowance of all the claims are requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson, Registration No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1050.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By

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